

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

of 30th July

To

Amarendra Amrend Advaites
B-47, Nizamuddin East
110033 New Delhi
India

PCT

NOTICE OF TRANSMITTAL OF
SUBSTANTIAL PRELIMINARY EXAMINATION
REPORT

PCT Rule 71.1j

29 JUN 2004

Applicant's or a legal representative's
reference

IMPORTANT NOTIFICATION

International Application No.

PCT/IN2003/000383

International Filing Date

3 December 2002

Priority Date

5 December 2003

Applicant

BIRON INDIA LIMITED et al

The applicant is hereby notified that the International Preliminary Examining Authority has issued the international preliminary examination report and the accompanying documents in the international application.

A copy of the report and its annexes is being transmitted to the International Bureau for communication to all the elected Offices.

Where required by any of the elected Offices, the International Examining Authority will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

REMINDER

The applicant must enter the national phase before each designated Office by performing certain acts (filing translations and paying national fees) within five months from the priority date of the international application (Article 39(1)(b) of the PCT). Please also the reminder sent by the International Bureau with form PCT/IS-P/01.


Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IP/EA/At

AUSTRALIAN PATENT OFFICE
PO BOX 200 WORMBEACH ACT 2696 AUSTRALIA
contact address: pct@ipaustralia.gov.au
Telephone No: 0821 6283 3923

Signature of the


IAN DOWD

Telephone No: 0821 6283 3923

PATENT COOPERATION TREATY
PCT
INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(Form PCT/ISPC/1999 No. 1)

Applicant's or agent's file reference
11/2424/1999

**FOR FURTHER
ACTION**

See Article 33 of the Regulations of the International Preliminary
Examination Authority (PCT/ISPC/1999, Article 33)

International Application No.

International filing date
01.06.2000

International filing date (local)

PCT/IN2000/00383

2 December 2000

2 December 2000

International Patent Classification (IPC) or other classification

Int. Cl. C07D 493/18

Applicant

RICKON INDIA LIMITED et al

1. This international preliminary examination report has been prepared by the International Preliminary Examining Authority and transmitted to the applicant according to Article 33.

2. This REPORT consists of a total of 2 sheets, including the front sheet.

- [X] This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and drawings which have been amended and are the basis for this report, and exhibits containing the citations made before the Authority (see Rule 10.16 and Section 907 of the Administrative Instructions under the PCT).

These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

- I. ☒ Basis of the report
- II. ☐ Priority
- III. ☐ Non establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV. ☐ Lack of unity of invention
- V. ☒ Reasoned statement under Article 35.2 with regard to novelty, inventive step and industrial applicability, citations and explanations supporting such statement
- VI. ☐ Certain documents cited
- VII. ☐ Certain defects in the international application
- VIII. ☐ Certain observations on the international application

Date of submission of the demand

22 March 2004

Date of completion of the report

24 June 2004

Name and mailing address of the IPHA A:

Author's address:

AUSTRALIAN PATENT OFFICE
PO BOX 240, WOOLLEN, ACT 2600, AUSTRALIA
E-mail address: ippe@ipaustralia.gov.au
Facsimile No.: 02 6265 9929

JAN DOWD

Telephone No.: 02 6265 9973

1. Basis of the report

With regard to the elements of the international application filed:

- ☒ the description: pages 2-7, consisting of:
 pages 1-3 filed with the demand;
 pages 1-7 received on 18 June 2004 and filed on 18 June 2004
- ☒ the claims: pages 9-10, consisting of:
 pages 1-2 submitted together with the demand and received on 18 June 2004;
 pages 1-3 filed with the demand;
 pages 8-10 received on 18 June 2004 and filed on 18 June 2004
- ☐ the drawings: page 1, as originally filed;
 pages 1-10, with the demand;
 pages 1-10 received on 18 June 2004
- ☐ the sequence listing part of the description:
 pages 1-3, as originally filed;
 pages 1-10, with the demand;
 pages 1-10 received on 18 June 2004

2. With regard to the language, if the elements marked above were a whole or furnished to the Authority in the language in which the international application was filed, unless they were indicated under this item these elements were available or furnished to the Authority in the following language, which is:

- ☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.4(a)).
- ☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 23.2 and 45.2).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form;
- ☐ filed together with the international application in computer readable form;
- ☐ furnished subsequently to this Authority in written form;
- ☐ furnished subsequently to this Authority in computer readable form;
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished;
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished;

4. ☐ The amendments have resulted in the cancellation of:

- ☐ the description: pages
- ☐ the claims: Nos.
- ☐ the drawings: sheets fig.

5. ☐ This report has been established as a notice of the amendments had not been made, since they have been considered to go beyond the disclosure as filed as indicated in the Supplementary (Rule 70.2(c)). **

Replaces word sheets which have been kept until the closing date in compliance with Article 24 are rejected from the search as "completely filed" and are not available for inspection, although they contain amendments (Rules 70.1(c) and 70.2).

For a preliminary search concerning a claim directed to a substance, which is not a chemical compound, see Rule 70.2(c)(ii).

V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability, citations and explanations supporting such statement

1 Statement

Novelty (A)	claim 1-10	YES
Inventive step (B)	claim 1-10	NO
Industrial applicability (C)	claim 1-10	YES
	claim 1-10	NO
Industrial applicability (C)	claim 1-10	YES
	claim 1-10	NO

2 Citations and explanations (Rule 70(2))

This report is based on the documents cited in the International Search Report.

D1 US 5,508,398 A1

D2 US 5,616,095 A1

D3 US 4,734,492 A1

D4 J. Antibiot. (Tokyo) 1999 May; 52(5): 316-77

D5 US 6,576,145 B1

D6 US 6,492,513 B1

Novelty and Inventive Step

None of the documents cited impinge on the application for the purposes of novelty or inventive step.

Industrial Applicability

All claims satisfy the requirements of industrial applicability.

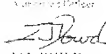
PATENT COOPERATION TREATY
PCT
INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 33, paragraph 2)

Applicant's file reference 11352(PCT/59)	FOR FURTHER ACTION		International Preliminary Examination Report Form PCT/ISA/220
International Application No. PCT/IN2003/000383	International Filing Date 2 December 2003	Priority Date (optional) 3 December 2003	
International Patent Classification (IPC) International Class. (optional)			
Int. Cl. ⁷ G 01 D 498 18			
Applicant BIOCON INDIA LIMITED et al			

1. This international preliminary examination report is drawn up by the International Preliminary Examining Authority and is transmitted to the applicant according to Article 33.
 2. This RPEA consists of a total of 3 sheets, including the cover sheet.
☒ This report is also accompanied by ANNEXes, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing amendments made before this Authority (see Rule 50.16 and Section 60 of the Administrative Instructions under the PCT).
 These annexes consist of a total of 3 sheets.
 3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Prior art
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 34(2) with regard to novelty, inventive step or industrial applicability, citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 22 March 2004	Date of completion of the report 24 June 2004
Name and mailing address of the IPEA AUSTRALIAN PATENT OFFICE PO BOX 200 WOODSIDE ACT 2606 AUSTRALIA E-mail address: ipc@ipaustralia.gov.au Facsimile No. (02) 6283 3028	Authorized Officer  IAN DOWD Telephone No. (02) 6283 3373

1. Basis of the report

With regard to the **elements** of the international application:

- ☐ the international application as originally filed
- ☒ the description: pages 2-7, as originally filed;
pages 1, filed with the demand;
pages 4, received on 18 June 2004 with the demand of 16 June 2003
- ☒ the claims: pages 9-10, as originally filed;
pages 1, 2, 3, amended together with the demand of 16 June 2003;
pages 1, filed with the demand;
pages 8, received on 18 June 2004 with the demand of 16 June 2003
- ☐ the drawings: pages 1, 2, 3, as originally filed;
pages 1, filed with the demand;
pages 1, received on 18 June 2004 with the demand of 16 June 2003
- ☐ the sequence listing part of the description:
pages 1, 2, 3, as originally filed;
pages 1, filed with the demand;
pages 1, received on 18 June 2004 with the demand of 16 June 2003

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: which is

- ☐ the language of a translation furnished for the purposes of international search under Rule 55.1(b);
- ☐ the language of publication of the international application under Rule 48.2(b);
- ☐ the language of the translation furnished for the purposes of international preliminary examination under Rules 55.2 and/or 55.3)

3. With regard to any **nucleotide and/or amino acid sequence disclosure** in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form;
- ☐ filed together with the international application in a machine-readable form;
- ☐ furnished subsequently to this Authority in written form;
- ☐ furnished subsequently to this Authority in computer-readable form;

☐ The statement that the information recorded in computer-readable form is identical to the written sequence listing has been furnished

☐ The statement that the information recorded in computer-readable form is identical to the written sequence listing has been furnished

4. ☐ The amendments have resulted in the cancellation of

- ☐ the description, pages
- ☐ the claims, Nos.
- ☐ the drawings, sheet(s)

5. ☐ This report has been established as a consequence of the amendments that have been made since they have been considered to go beyond the disclosure as filed, as indicated in the Supplementary Bulletin, 2004/12/15.

Replacement sheets which have been furnished in the form of a CD-ROM or in another machine-readable form are referred to in this report as "originally filed" and are not attached to this report. The replacement sheets, amendments filed on 16 June and 18 June 2004.

The replacement sheet containing such amendments is attached to this report and is not considered as part of the report.

VI. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability: citations and explanations supporting such statement:

1. Summary

Novelty (N)	Claims 1-10	YES
	Claims	NO
Inventive step (IS)	Claims 1-10	YES
	Claims	NO
Industrial applicability (IA)	Claims 1-10	YES
	Claims	NO

2. Citations and explanations (Rule 70(1))

This report is based on the documents cited in the International Search Report:

- D1 US 5 308 798 A1
- D2 US 6 636 595 A1
- D3 US 4 732 497 A1
- D4 J. Antibiot (Tokyo) 1999 May, 52(5): 469-73
- D5 US 6 376 135 B1
- D6 US 6 497 513 B1

Novelty and Inventive Step

None of the documents cited impinge on the application for the purposes of novelty or inventive step

Industrial Applicability

All claims satisfy the requirements of industrial applicability

5 **TITLE OF THE INVENTION**

PROCESS FOR THE PURIFICATION OF MACROLIDES

FIELD OF THE INVENTION

This invention relates to a process for purification of macrolides.

10 **BACKGROUND OF THE INVENTION**

A compound, 15,19-Epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone, 5,6,8,11,12,13,14,15,16,17,18,19,24,25, 26,26a-hexadecahydro-5,19-dihydroxy-3-[(1E)-2-[(1R,3R,4R)-4-hydroxy-3-methoxycyclohexyl]-1-methyl ethenyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-8-(2-propenyl)-, (3S,4R,5S,8R,9E,12S,14S,15R,16S,18R,19R,26aS), also known as FK506 as well as tacrolimus disclosed by EP 184162 and US 4,894,366 is useful as an immunosuppressant. Another compound, 20 15,19-Epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone,8-ethyl-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26, 26a-hexadecahydro-5,19-dihydroxy-3-[(1E)-2-[(1R,3R,4R)-4-hydroxy-3-methoxycyclohexyl]-1-methylethenyl]-14,16-dimethoxy-4,10,12,18-25 tetramethyl-, (3S,4R,5S,8R,9E,12S,14S, 15R,16S,18R,19R,26aS)-, also known as immunomycin as well as FK 520, disclosed in EPO Publication No. 0184162 is also useful as an immunosuppressant. Many other derivatives of these compounds as well as structural analogues have immunosuppressant property.

30

5 We claim:

1. A process for the recovery of a macrolide in substantially
pure form comprising:
 - a) treatment of an impure or crude macrolide with water
immiscible solvent,
 - 10 b) optional concentration of the mixture,
 - c) treatment with ammonia gas to phase out impurities,
 - d) separation of impurities,
 - e) optional concentration of the phase containing the
macrolide,
 - 15 f) loading on silica gel chromatography, optionally
reversed phase or pretreated with silver, and elution of
the macrolide,
 - g) affording the macrolide in substantially pure form,
 - h) optional repetition of step f and g to afford the
macrolide in substantially pure form.
- 20 2. A process as in claim 1, wherein the macrolide is selected
from tacrolimus, immunomycin or sirolimus.
3. A process as in claim 1, wherein the water immiscible solvent
is selected from a group comprising hydrocarbons,
25 heterocyclic compounds, ethers or esters.
4. A process as in claim 1, wherein the water immiscible
solvents is selected from a group comprising benzene,
toluene, hexane, ethyl acetate, isobutyl acetate or butyl
acetate.
- 30 5. A process as in claim 1, wherein the macrolide compound is
afforded by crystallization or precipitation.